CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65002

APPROVAL LETTER

ANDA 65-002

SEP 28 1998

American Pharmaceutical Partners, Inc.
Attention: Lincy Michael
2045 North Cornell Avenue
Melrose Park, IL 60160

Dear Madam:

This is in reference to your abbreviated new drug application dated December 16, 1997, submitted pursuant to Section 505(j) of the Federal Food, Drug, and Cosmetic Act, for Cefuroxime for Injection USP, 7.5 g (Pharmacy Bulk Package). We note that this product is subject to the exception provisions of Section 125(d)(2) of Title I of the Food and Drug Administration Modernization Act of 1997.

Reference is also made to your amendments dated January 20, February 26, June 1, 2, and 11, July 10, and 30, and September 24, 1998.

We have completed the review of this abbreviated application and have concluded that the drug is safe and effective for use as recommended in the submitted labeling. Accordingly, the application is approved. The Division of Bioequivalence has determined your Cefuroxime for Injection USP, 7.5 g (Pharmacy Bulk Package) to be bioequivalent and, therefore, therapeutically equivalent to the listed drug [Zinacef® Injection 7.5 g, (Pharmacy Bulk Package), of Glaxo Wellcome, Inc.].

Under 21 CFR 314.70, certain changes in the conditions described in this abbreviated application require an approved supplemental application before the change may be made.

Post-marketing reporting requirements for this abbreviated application are set forth in 21 CFR 314.80-81 and 314.98. The Office of Generic Drugs should be advised of any change in the marketing status of this drug.

We request that you submit, in duplicate, any proposed advertising or promotional copy which you intend to use in your initial advertising or promotional campaigns. Please submit all proposed materials in draft or mock-up form, not final print.

Submit both copies together with a copy of the proposed or final printed labeling to the Division of Drug Marketing, Advertising, and Communications (HFD-40). Please do not use Form FD-2253 (Transmittal of Advertisements and Promotional Labeling for Drugs for Human Use) for this initial submission.

We call your attention to 21 CFR 314.81(b)(3) which requires that materials for any subsequent advertising or promotional campaign be submitted to our Division of Drug Marketing, Advertising, and Communications (HFD-40) with a completed Form FD-2253 at the time of their initial use.

Sincerely yours,

/S/

Douglas L. Sporn
Director
Office of Generic Drugs
Center for Drug Evaluation and Research

9-28-98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65002

DRAFT FINAL PRINTED LABELING

AMERICAN PHARMACEUTICAL PARTNERS, INC.

APPROVED

SEP 28 1998

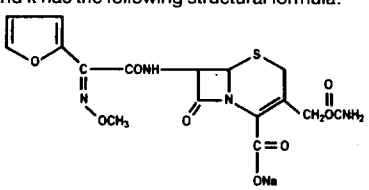
45651/Issued: June 1998

CEFUROXIME

FOR INJECTION, USP

PHARMACY BULK PACKAGE–
Not for Direct Infusion

DESCRIPTION:
Cefuroxime is a semisynthetic, broad-spectrum, cephalosporin antibiotic for parenteral administration. It is the sodium salt of (6R, 7R)-3-carbamoyloxymethyl-7-[Z-2-methoxyimino-2-(fur-2-yl) acetamido]ceph-3-em-4-carboxylate, and it has the following structural formula:



$C_{16}H_{15}N_4NaO_8S$ **M.W. 446.38**

Cefuroxime for Injection, USP contains approximately 54.2 mg (2.4 mEq) of sodium per gram of cefuroxime activity.

Cefuroxime for Injection, USP is a sterile, dry, white to light yellow crystalline powder supplied in pharmacy bulk packages equivalent to 7.5 g of cefuroxime as cefuroxime sodium. Solutions of Cefuroxime for Injection, USP range in color from light yellow to amber, depending on the concentration and diluent used. The pH of freshly constituted solutions usually ranges from 6 to 8.5.

A pharmacy bulk package is a container of a sterile preparation for parenteral use that contains many single doses. The contents are intended for use in a pharmacy admixture service and are restricted to the preparation of admixtures for intravenous infusion. FURTHER DILUTION IS REQUIRED BEFORE USE.

CLINICAL PHARMACOLOGY:
After intramuscular (IM) injection of a 750 mg dose of cefuroxime to normal volunteers, the mean peak serum concentration was 27 mcg/mL. The peak occurred at approximately 45 minutes (range, 15 to 60 minutes). Following intravenous (IV) doses of 750 mg and 1.5 g, serum concentrations were approximately 50 and 100 mcg/mL, respectively, at 15 minutes. Therapeutic serum concentrations of approximately 2 mcg/mL or more were maintained for 5.3 hours and 8 hours or more, respectively. There was no evidence of accumulation of cefuroxime in the serum following IV administration of 1.5 g doses every 8 hours to normal volunteers. The serum half-life after either IM or IV injections is approximately 80 minutes.

Approximately 89% of a dose of cefuroxime is excreted by the kidneys over an 8-hour period, resulting in high urinary concentrations.

Following the IM administration of a 750 mg single dose, urinary concentrations averaged 1,300 mcg/mL during the first 8 hours. Intravenous doses of 750 mg and 1.5 g produced urinary levels averaging 1,150 and 2,500 mcg/mL, respectively, during the first 8-hour period.

The concomitant oral administration of probenecid with cefuroxime slows tubular secretion, decreases renal clearance by approximately 40%, increases the peak serum level by approximately 30%, and increases the serum half-life by approximately 30%. Cefuroxime is detectable in therapeutic concentrations in pleural fluid, joint fluid, bile, sputum, bone, and aqueous humor.

Cefuroxime is detectable in therapeutic concentrations in cerebrospinal fluid (CSF) of adults and pediatric patients with meningitis. The following table shows the concentrations of cefuroxime achieved in cerebrospinal fluid during multiple dosing of patients with meningitis.

Patients	Dose	Number of Patients	Mean (Range) CSF Cefuroxime Concentrations (mcg/mL) Achieved Within 8 Hours Post Dose
Pediatric patients (4 weeks to 6.5 years)	200 mg/kg/day divided q 6 hours	5	6.6 (0.9-17.3)
Pediatric patients (7 months to 9 years)	200 to 230 mg/kg/day divided q 8 hours	6	8.3 (<2-22.5)
Adults	1.5 grams q 8 hours	2	5.2 (2.7-8.9)
Adults	1.5 grams q 6 hours	10	6 (1.5-13.5)

Cefuroxime is approximately 50% bound to serum protein.

Microbiology
Cefuroxime has *in vitro* activity against a wide range of gram-positive and gram-negative organisms, and it is highly stable in the presence of beta-lactamases of certain gram-negative bacteria. The bactericidal action of cefuroxime results from inhibition of cell-wall synthesis.

Cefuroxime is usually active against the following organisms *in vitro*.

Aerobes, Gram-positive
Staphylococcus aureus, Staphylococcus epidermidis, Streptococcus pneumoniae, and *Streptococcus pyogenes* (and other streptococci). NOTE: Most strains of enterococci, e.g., *Enterococcus faecalis* (formerly *Streptococcus faecalis*), are resistant to cefuroxime. Methicillin-resistant staphylococci and *Listeria monocytogenes* are resistant to cefuroxime.

Aerobes, Gram-negative
Citrobacter spp., *Enterobacter* spp., *Escherichia coli, Haemophilus influenzae* (including ampicillin-resistant strains), *Haemophilus parainfluenzae, Klebsiella* spp. (including *Klebsiella pneumoniae*), *Moraxella* (*Branhamella*) *catarrhalis* (including ampicillin- and cephalothin-resistant strains), *Morganella morganii* (formerly *Proteus morganii*), *Neisseria gonorrhoeae* (including penicillinase- and non-penicillinase-producing strains), *Neisseria meningitidis, Proteus mirabilis, Providencia rettgeri* (formerly *Proteus rettgeri*), *Salmonella* spp., and *Shigella* spp. NOTE: Some strains of *Morganella morganii, Enterobacter cloacae*, and *Citrobacter* spp. have been shown by *in vitro* tests to be resistant to cefuroxime and other cephalosporins. *Pseudomonas* and *Campylobacter* spp., *Acinetobacter calcoaceticus*, and most strains of *Serratia* spp. and *Proteus vulgaris* are resistant to most first- and second-generation cephalosporins.

Anaerobes
Gram-positive and gram-negative cocci (including *Peptococcus* and *Peptostreptococcus* spp.), gram-positive bacilli (including *Clostridium* spp.), and gram-negative bacilli (including *Bacteroides* and *Fusobacterium* spp.). NOTE: *Clostridium difficile* and most strains of *Bacteroides fragilis* are resistant to cefuroxime.

Susceptibility Tests
Diffusion Techniques
Quantitative methods that require measurement of zone diameters give an estimate of antibiotic susceptibility. One such standard procedure[1] that has been recommended for use with disks to test susceptibility of organisms to cefuroxime uses the 30 mcg cefuroxime disk. Interpretation involves the correlation of the diameters obtained in the disk test with the minimum inhibitory concentration (MIC) for cefuroxime.

A report of "Susceptible" indicates that the pathogen is likely to be inhibited by generally achievable blood levels. A report of "Moderately Susceptible" suggests that the organism would be susceptible if high dosage is used or if the infection is confined to tissues and fluids in which high antibiotic levels are attained. A report of "Intermediate" suggests an equivocal or indeterminate result. A report of "Resistant" indicates that achievable concentrations of the antibiotic are unlikely to be inhibitory and other therapy should be selected.

Reports from the laboratory giving results of the standard single-disk susceptibility test for organisms other than *Haemophilus* spp. and *Neisseria gonorrhoeae* with a 30 mcg cefuroxime disk should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 18	(S) Susceptible
15-17	(MS) Moderately Susceptible
≤ 14	(R) Resistant

Results for *Haemophilus* spp. should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 24	(S) Susceptible
21-23	(I) Intermediate
≤ 20	(R) Resistant

Results for *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

Zone Diameter (mm)	Interpretation
≥ 31	(S) Susceptible
26-30	(MS) Moderately Susceptible
≤ 25	(R) Resistant

Organisms should be tested with the cefuroxime disk since cefuroxime has been shown by *in vitro* tests to be active against certain strains found resistant when other beta-lactam disks are used. The cefuroxime disk should not be used for testing susceptibility to other cephalosporins.

Standardized procedures require the use of laboratory control organisms. The 30 mcg cefuroxime disk should give the following zone diameters.

1. Testing for organisms other than *Haemophilus* spp. and *Neisseria gonorrhoeae*:

Organism	Zone Diameter (mm)
Staphylococcus aureus ATCC 25923	27-35
Escherichia coli ATCC 25922	20-26

2. Testing for *Haemophilus* spp:

Organism	Zone Diameter (mm)
Haemophilus influenzae ATCC 49766	28-36

3. Testing for *Neisseria gonorrhoeae*:

Organism	Zone Diameter (mm)
Neisseria gonorrhoeae ATCC 49226	33-41
Staphylococcus aureus ATCC 25923	29-33

Dilution Techniques: Use a standardized dilution method[1] (broth, agar, microdilution) or equivalent with cefuroxime powder. The MIC values obtained for bacterial isolates other than *Haemophilus* spp. and *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 8	(S) Susceptible
16	(MS) Moderately Susceptible
≥ 32	(R) Resistant

MIC values obtained for *Haemophilus* spp. should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 4	(S) Susceptible
8	(I) Intermediate
≥ 16	(R) Resistant

MIC values obtained for *Neisseria gonorrhoeae* should be interpreted according to the following criteria:

MIC (mcg/mL)	Interpretation
≤ 1	(S) Susceptible
2	(MS) Moderately Susceptible
≥ 4	(R) Resistant

As with standard diffusion techniques, dilution methods require the use of laboratory control organisms. Standard cefuroxime powder should provide the following MIC values.

1. For organisms other than *Haemophilus* spp. and *Neisseria gonorrhoeae*:

Organism	MIC (mcg/mL)
Staphylococcus aureus ATCC 29213	0.5-2.0
Escherichia coli ATCC 25922	2.0-8.0

2. For *Haemophilus* spp.:

Organism	MIC (mcg/mL)
Haemophilus influenzae ATCC 49766	0.25-1.0

3. For *Neisseria gonorrhoeae*:

Organism	MIC (mcg/mL)
Neisseria gonorrhoeae ATCC 49226	0.25-1.0
Staphylococcus aureus ATCC 29213	0.25-1.0

INDICATIONS AND USAGE:
Cefuroxime for Injection is indicated for the treatment of patients with infections caused by susceptible strains of the designated organisms in the following diseases:

1. **Lower Respiratory Tract Infections**, including pneumonia, caused by *Streptococcus pneumoniae*, *Haemophilus influenzae* (including ampicillin-resistant strains), *Klebsiella* spp., *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains), *Streptococcus pyogenes*, and *Escherichia coli*.
2. **Urinary Tract Infections** caused by *Escherichia coli* and *Klebsiella* spp.
3. **Skin and Skin-Structure Infections** caused by *Staphylococcus aureus* (penicillinase- and non-pencillinase-producing strains), *Streptococcus pyogenes, Escherichia coli, Klebsiella* spp., and *Enterobacter* spp.
4. **Septicemia** caused by *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains), *Streptococcus pneumoniae, Escherichia coli, Haemophilus influenzae,* (including ampicillin-resistant strains), and *Klebsiella* spp.
5. **Meningitis** caused by *Streptococcus pneumoniae, Haemophilus influenzae,* (including ampicillin-resistant strains), *Neisseria meningitidis*, and *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains).
6. **Gonorrhea:** Uncomplicated and disseminated gonococcal infections due to *Neisseria gonorrhoeae* (penicillinase- and non-penicillinase-producing strains) in both males and females.
7. **Bone and Joint Infections** caused by *Staphylococcus aureus* (penicillinase- and non-penicillinase-producing strains).

Clinical microbiological studies in skin and skin structure infections frequently reveal the growth of susceptible strains of both aerobic and anaerobic organisms. Cefuroxime for Injection has been used successfully in these mixed infections in which several organisms have been isolated. Appropriate cultures and susceptibility studies should be performed to determine the susceptibility of the causative organisms to Cefuroxime for Injection.

Therapy may be started while awaiting the results of these studies; however, once these results become available, the antibiotic treatment should be adjusted accordingly. In certain cases of confirmed or suspected gram-positive or gram-negative sepsis or in patients with other serious infections in which the causative organism has not been identified, Cefuroxime for Injection may be used concomitantly with an aminoglycoside (see **PRECAUTIONS**). The recommended doses of both antibiotics may be given depending on the severity of the infection and the patient's condition.

Prevention

The preoperative prophylactic administration of Cefuroxime for Injection may prevent the growth of susceptible disease-causing bacteria and thereby may reduce the incidence of certain postoperative infections in patients undergoing surgical procedures (e.g., vaginal hysterectomy) that are classified as clean-contaminated or potentially contaminated procedures. Effective prophylactic use of antibiotics in surgery depends on the time of administration. Cefuroxime for Injection should usually be given one-half to 1 hour before the operation to allow sufficient time to achieve effective antibiotic concentrations in the wound tissues during the procedure. The dose should be repeated intraoperatively if the surgical procedure is lengthy.

Prophylactic administration is usually not required after the surgical procedure ends and should be stopped within 24 hours. In the majority of surgical procedures, continuing prophylactic administration of any antibiotic does not reduce the incidence of subsequent infections but will increase the possibility of adverse reactions and the development of bacterial resistance.

The perioperative use of Cefuroxime for Injection has also been effective during open heart surgery for surgical patients in whom infections at the operative site would present a serious risk. For these patients it is recommended that Cefuroxime for Injection therapy be continued for at least 48 hours after the surgical procedure ends. If an infection is present, specimens for culture should be obtained for the identification of the causative organism, and appropriate antimicrobial therapy should be instituted.

CONTRAINDICATIONS:
Cefuroxime for Injection is contraindicated in patients with known allergy to the cephalosporin group of antibiotics.

WARNINGS:
BEFORE THERAPY WITH CEFUROXIME FOR INJECTION IS INSTITUTED, CAREFUL INQUIRY SHOULD BE MADE TO DETERMINE WHETHER THE PATIENT HAS HAD PREVIOUS HYPERSENSITIVITY REACTIONS TO CEPHALOSPORINS, PENICILLINS, OR OTHER DRUGS. THIS PRODUCT SHOULD BE GIVEN CAUTIOUSLY TO PENICILLIN-SENSITIVE PATIENTS. ANTIBIOTICS SHOULD BE ADMINISTERED WITH CAUTION TO ANY PATIENT WHO HAS DEMONSTRATED SOME FORM OF ALLERGY, PARTICULARLY TO DRUGS. IF AN ALLERGIC REACTION TO CEFUROXIME FOR INJECTION OCCURS, DISCONTINUE THE DRUG. SERIOUS ACUTE HYPERSENSITIVITY REACTIONS MAY REQUIRE EPINEPHRINE AND OTHER EMERGENCY MEASURES.

Pseudomembranous colitis has been reported with nearly all antibacterial agents, including cefuroxime, and may range in severity from mild to life threatening. Therefore, it is important to consider this diagnosis in patients who present with diarrhea subsequent to the administration of antibacterial agents.

Treatment with antibacterial agents alters the normal flora of the colon and may permit overgrowth of clostridia. Studies indicate that a toxin produced by *Clostridium difficile* is one primary cause of antibiotic-associated colitis.

After the diagnosis of pseudomembranous colitis has been established, appropriate therapeutic measures should be initiated. Mild cases of pseudomembranous colitis usually respond to drug discontinuation alone. In moderate to severe cases, consideration should be given to management with fluids and electrolytes, protein supplementation, and treatment with an antibacterial drug clinically effective against *Clostridium difficile* colitis.

When the colitis is not relieved by drug discontinuation or when it is severe, oral vancomycin is the treatment of choice for antibiotic-associated pseudomembranous colitis

produced by *Clostridium difficile*. Other causes of colitis should also be considered.

PRECAUTIONS:
Although Cefuroxime for Injection rarely produces alterations in kidney function, evaluation of renal status during therapy is recommended, especially in seriously ill patients receiving the maximum doses. Cephalosporins should be given with caution to patients receiving concurrent treatment with potent diuretics as these regimens are suspected of adversely affecting renal function.

The total daily dose of Cefuroxime for Injection should be reduced in patients with transient or persistent renal insufficiency (see **DOSAGE AND ADMINISTRATION**), because high and prolonged serum antibiotic concentrations can occur in such individuals from usual doses.

As with other antibiotics, prolonged use of Cefuroxime for Injection may result in overgrowth of nonsusceptible organisms. Careful observation of the patient is essential. If superinfection occurs during therapy, appropriate measures should be taken.

Broad-spectrum antibiotics should be prescribed with caution in the individuals with a history of gastrointestinal disease, particularly colitis.

Nephrotoxicity has been reported following concomitant administration of aminoglycoside antibiotics and cephalosporins.

As with other therapeutic regimens used in the treatment of meningitis, mild to severe hearing loss has been reported in some pediatric patients treated with cefuroxime sodium. Persistence of positive CSF (cerebrospinal fluid) cultures at 18 to 36 hours, particularly in patients with *Haemophilus influenzae* isolates, has also been noted; however, the precise clinical impact of this is unknown.

Drug/Laboratory Test Interactions
A false-positive reaction for glucose in the urine may occur with copper reduction tests (Benedict's or Fehling's solution or with Clinitest® tablets) but not with enzyme-based tests for glycosuria (e.g., Tes-Tape®). As a false-negative result may occur in the ferricyanide test, it is recommended that either the glucose oxidase or hexokinase method be used to determine blood plasma glucose levels in patients receiving Cefuroxime for Injection.

Cefuroxime does not interfere with the assay of serum and urine creatinine by the alkaline picrate method.

Carcinogenesis, Mutagenesis, Impairment of Fertility
Although no long-term studies in animals have been performed to evaluate carcinogenic potential, no mutagenic potential of cefuroxime was found in standard laboratory tests.

Reproductive studies revealed no impairment of fertility in animals.

Pregnancy: Teratogenic Effects: Pregnancy Category B
Reproduction studies have been performed in mice and rabbits at doses up to 60 times the human dose and have revealed no evidence of impaired fertility or harm to the fetus due to cefuroxime. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed.

Nursing Mothers
Since cefuroxime is excreted in human milk, caution should be exercised when Cefuroxime for Injection is administered to a nursing woman.

Pediatric Use
Safety and effectiveness in pediatric patients below 3 months of age have not been established. Accumulation of other members of the cephalosporin class in newborn infants (with resulting prolongation of drug half-life) has been reported.

ADVERSE REACTIONS:
Cefuroxime for Injection is generally well tolerated. The most common adverse effects have been local reactions following IV administration. Other adverse reactions have been encountered only rarely.

Local Reactions
Thrombophlebitis has occurred with IV administration in 1 in 60 patients.

Gastrointestinal
Gastrointestinal symptoms occurred in 1 in 150 patients and included diarrhea (1 in 220 patients) and nausea (1 in 440 patients). Onset of pseudomembranous colitis symptoms may occur during or after antibiotic treatment (see **WARNINGS**).

Hypersensitivity Reactions
Hypersensitivity reactions have been reported in fewer than 1% of the patients treated with Cefuroxime for Injection and include rash (1 in 125). Pruritus, urticaria, and positive Coombs' test each occurred in fewer than 1 in 250 patients, and, as with other cephalosporins, rare cases of anaphylaxis, drug fever, erythema multiforme, interstitial nephritis, toxic epidermal necrolysis, and Stevens-Johnson syndrome have occurred.

Blood
A decrease in hemoglobin and hematocrit has been observed in 1 in 10 patients and transient eosinophilia in 1 in 14 patients. Less common reactions seen were transient neutropenia (fewer than 1 in 100 patients) and leukopenia (1 in 750 patients). A similar pattern and incidence were seen with other cephalosporins used in controlled studies. As with other cephalosporins, there have been rare reports of thrombocytopenia.

Hepatic
Transient rise in SGOT and SGPT (1 in 25 patients), alkaline phosphatase (1 in 50 patients), LDH (1 in 75 patients), and bilirubin (1 in 500 patients) levels has been noted.

Kidney
Elevations in serum creatinine and/or blood urea nitrogen and a decreased creatinine clearance have been observed, but their relationship to cefuroxime is unknown.

In addition to the adverse reactions listed above that have been observed in patients treated with cefuroxime, the following adverse reactions and altered laboratory tests have been reported for cephalosporin-class antibiotics:

Adverse Reactions-Vomiting, abdominal pain, colitis, vaginitis including vaginal candidiasis, toxic nephropathy, hepatic dysfunction including cholestasis, aplastic anemia, hemolytic anemia, hemorrhage.

Several cephalosporins have been implicated in triggering seizures, particularly in patients with renal impairment when the dosage was not reduced (see **DOSAGE AND ADMINISTRATION**). If seizures associated with drug therapy should occur, the drug should be discontinued. Anticonvulsant therapy can be given if clinically indicated.

Altered Laboratory Tests-Prolonged prothrombin time, pancytopenia, agranulocytosis.

OVERDOSAGE:
Overdosage of cephalosporins can cause cerebral irritation leading to convulsions. Serum levels of cefuroxime can be reduced by hemodialysis and peritoneal dialysis.

DOSAGE AND ADMINISTRATION:

The intent of this pharmacy bulk package is for the preparation of solutions for intravenous infusion only. Dosing references to the intramuscular route of administration are for informational purposes only.

Dosage

Adults

The usual adult dosage range for Cefuroxime for Injection is 750 mg to 1.5 grams every 8 hours, usually for 5 to 10 days. In uncomplicated urinary tract infections, skin and skin-structure infections, disseminated gonococcal infections, and uncomplicated pneumonia, a 750 mg dose every 8 hours is recommended. In severe or complicated infections, a 1.5 gram dose every 8 hours is recommended.

In bone and joint infections, a 1.5 gram dose every 8 hours is recommended. In clinical trials, surgical intervention was performed when indicated as an adjunct to Cefuroxime for Injection therapy. A course of oral antibiotics was administered when appropriate following the completion of parenteral administration of Cefuroxime for Injection.

In life-threatening infections or infections due to less susceptible organisms, 1.5 grams every 6 hours may be required. In bacterial meningitis, the dosage should not exceed 3 grams every 8 hours. The recommended dosage for uncomplicated gonococcal infection is 1.5 grams given intramuscularly as a single dosage at two different sites together with 1 gram of oral probenecid. For preventive use for clean-contaminated or potentially contaminated surgical procedures, a 1.5 gram dose administered intravenously just before surgery (approximately one-half to 1 hour before the initial incision) is recommended. Thereafter, give 750 mg intravenously or intramuscularly every 8 hours when the procedure is prolonged.

For preventive use during open heart surgery, a 1.5 gram dose administered intravenously at the induction of anesthesia and every 12 hours thereafter for a total of 6 grams is recommended.

Impaired Renal Function

A reduced dosage must be employed when renal function is impaired. Dosage should be determined by the degree of renal impairment and the susceptibility of the causative organism (see Table 1).

Table 1:
Dosage of Cefuroxime for Injection in Adults with Reduced Renal Function

Creatinine Clearance (mL/min)	Dose	Frequency
>20	750 mg to 1.5 grams	q8h
10-20	750 mg	q12h
<10	750 mg	q24h*

*Since Cefuroxime for Injection is dialyzable, patients on hemodialysis should be given a further dose at the end of the dialysis.

When only serum creatinine is available, the following formula[2] (based on sex, weight, and age of the patient) may be used to convert this value into creatinine clearance. The serum creatinine should represent a steady state of renal function.

$$\text{Males: Creatinine clearance (mL/min)} = \frac{\text{Weight (kg)} \times (140 - \text{age})}{72 \times \text{serum creatinine (mg/dL)}}$$

Females: 0.85 x male value

Note: As with antibiotic therapy in general, administration of Cefuroxime for Injection should be continued for a minimum of 48 to 72 hours after the patient becomes asymptomatic or after evidence of bacterial eradication has been obtained; a minimum of 10 days of treatment is recommended in infections caused by *Streptococcus pyogenes* in order to guard against the risk of rheumatic fever or glomerulonephritis; frequent bacteriologic and clinical appraisal is necessary during therapy of chronic urinary tract infection and may be required for several months after therapy has been completed; persistent infections may require treatment for several weeks; and doses smaller than those indicated above should not be used. In staphylococcal and other infections involving a collection of pus, surgical drainage should be carried out where indicated.

Pediatric Patients Above 3 Months of Age

Administration of 50 to 100 mg/kg per day in equally divided doses every 6 to 8 hours has been successful for most infections susceptible to cefuroxime. The higher dosage of 100 mg/kg per day (not to exceed the maximum adult dosage) should be used for the more severe or serious infections.

In bone and joint infections, 150 mg/kg per day (not to exceed the maximum adult dosage) is recommended in equally divided doses every 8 hours. In clinical trials, a course of oral antibiotics was administered to pediatric patients following the completion of parenteral administration of Cefuroxime for Injection.

In cases of bacterial meningitis, a larger dosage of Cefuroxime for Injection is recommended, 200 to 240 mg/kg per day intravenously in divided doses every 6 to 8 hours.

In pediatric patients with renal insufficiency, the frequency of dosing should be modified consistent with the recommendations for adults.

Preparation of Solution

The 7.5 gram pharmacy bulk package should be constituted with 77 mL of sterile water for injection; each 8 mL of the resulting solution contains 750 mg of cefuroxime.

Table 2: Preparation of Solution

Strength	Amount of Diluent to Be Added (mL)	Volume to Be Withdrawn	Approximate Cefuroxime Concentration (mg/mL)
7.5 gram Pharmacy bulk package	77	Amount Needed*	95

*8 mL of solution contains 750 mg of cefuroxime; 16 mL of solution contains 1.5 grams of cefuroxime

Administration

Intravenous Administration

The IV route may be preferable for patients with bacterial septicemia or other severe or life-threatening infections or for patients who may be poor risks because of lowered resistance, particularly if shock is present or impending.

For intermittent IV infusion with a Y-type administration set, dosing can be accomplished through the tubing system by which the patient may be receiving other IV solutions. However, during infusion of the solution containing Cefuroxime for Injection, it is advisable to temporarily discontinue administration of any other solutions at the same site.

For continuous IV infusion, a solution of Cefuroxime for Injection may be added to an IV container of one of the following fluids: 0.9% sodium chloride injection; 5% dextrose injection; 10% dextrose injection; 5% dextrose and 0.9% sodium chloride injection; 5% dextrose and 0.45% sodium chloride injection; or 1/6 M sodium lactate injection.

Solutions of Cefuroxime for Injection, like those of most beta-lactam antibiotics, should not be added to solutions of aminoglycoside antibiotics because of potential interaction.

However, if concurrent therapy with Cefuroxime for Injection and an aminoglycoside is indicated, each of these antibiotics can be administered separately to the same patient.

Compatibility and Stability

The 7.5 g pharmacy bulk package vials are to be constituted as directed with sterile water for injection, the withdrawal of container contents should be completed within 4 hours. More dilute solutions, such as 750 mg or 1.5 g plus 100 mL of sterile water for injection, 5% dextrose injection, or 0.9% sodium chloride injection, also maintain satisfactory potency for 24 hours at room temperature and for 7 days under refrigeration.

These solutions may be further diluted to concentrations of between 1 and 30 mg/mL in the following solutions and will lose not more than 10% activity for 24 hours at room temperature or at least 7 days under refrigeration: 0.9% sodium chloride injection; 1/6 M sodium lactate injection; ringer's injection, USP; lactated ringer's injection, USP; 5% dextrose and 0.9% sodium chloride injection; 5% dextrose injection; 5% dextrose and 0.45% sodium chloride injection; 5% dextrose and 0.225% sodium chloride injection; 10% dextrose injection; and 10% invert sugar in water for injection.

Unused solutions should be discarded after the time periods mentioned above.

Cefuroxime for Injection has also been found compatible for 24 hours at room temperature when admixed in IV infusion with heparin (10 and 50 U/mL) in 0.9% sodium chloride injection and potassium chloride (10 and 40 mEq/L) in 0.9% sodium chloride injection. Sodium bicarbonate injection, USP is not recommended for the dilution of Cefuroxime for Injection.

Frozen Stability

Constitute the 7.5 g Pharmacy Bulk Package as directed for intravenous administration in Table 2. Immediately withdraw 8 or 16 mL from the 7.5 g bulk vial and add to 50 or 100 mL of 0.9% sodium chloride injection or 5% dextrose injection and freeze. Frozen solutions are stable for 6 months when stored at -20°C. Frozen solutions should be thawed at room temperature and not refrozen. Do not force thaw by immersion in water baths or by microwave irradiation. Thawed solutions may be stored for up to 24 hours at room temperature or for 7 days in a refrigerator.

Note: Parenteral drug products should be inspected visually for particulate matter and discoloration before administration whenever solution and container permit.

As with other cephalosporins, Cefuroxime for Injection powder as well as solutions tend to darken, depending on storage conditions, without adversely affecting product potency.

Directions for Dispensing: Pharmacy Bulk Package–Not for Direct Infusion: Using aseptic technique, the container closure may be penetrated only one time, utilizing a suitable sterile transfer device or dispensing set which allows measured distribution of the contents. Use of this product is restricted to a suitable work area, such as a laminar flow hood. The use of syringe and needle is not recommended as it may cause leakage.

The withdrawal of container contents should be accomplished without delay. However, should this not be possible, a maximum time of 4 hours from initial closure entry is permitted to complete fluid transfer operations. This time limit should begin with the introduction of solvent or diluent into the Pharmacy Bulk Package.

After reconstitution: Use promptly. DISCARD VIAL WITHIN 4 HOURS AFTER INITIAL ENTRY.

HOW SUPPLIED:

Cefuroxime for Injection, USP in the dry state should be stored between 15° and 30°C (59° and 86°F) and protected from light. Cefuroxime for Injection, USP is supplied as follows:

Product No.	NDC No.	
301361	63323-313-61	Cefuroxime sodium equivalent to 7.5 g cefuroxime in a 100 mL Pharmacy Bulk Package (tray of 10).

Rx only

REFERENCES:

1. National Committee for Clinical Laboratory Standards. *Performance Standards for Antimicrobial Susceptibility Testing*. Third Informational Supplement. NCCLS Document M100-S3, Vol. 11, No. 17. Villanova, PA: NCCLS; 1991.
2. Cockcroft DW, Gault MH: Prediction of creatinine clearance from serum creatinine. *Nephron*. 1976;16:31-41.

AMERICAN PHARMACEUTICAL PARTNERS, INC.
Santa Monica, CA 90404

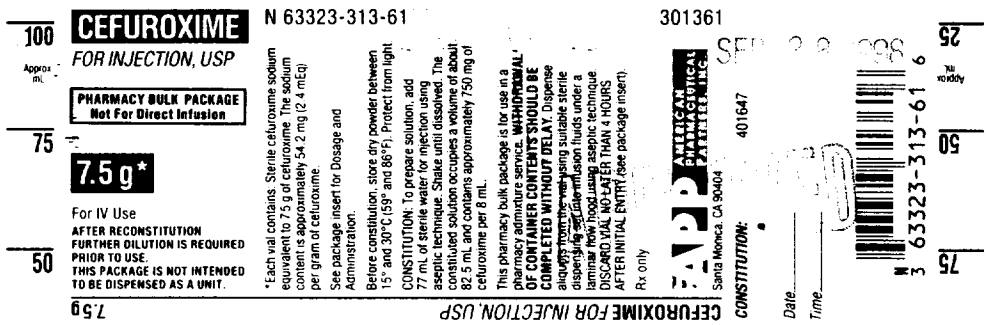
45651
Issued: June 1998

Mango 000 00059

ANDA 65-002
Cefuroxime for Injection, USP (PBP)

CONTAINER LABEL

7.5 g / vial



CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65002

CHEMISTRY REVIEW(S)

ANDA APPROVAL SUMMARY

ANDA #: 65-002 **DRUG PRODUCT:** Sterile Cefuroxime Sodium USP

FIRM: American Pharmaceutical Partners, Inc. (Formerly Fujisawa USA, Inc.)

DOSAGE: Sterile powder for injection

STRENGTH: 7.5 g base/vial in Pharmacy Bulk Package

CAMP STATEMENT/EIR UPDATE STATUS: Acceptable 2/17/98.

BIO STUDY: Bio waiver is granted (3/27/98).

METHOD VALIDATION - (DESCRIPTION OF DOSAGE FORM SAME AS FIRM'S): Not requested (USP drug)

STABILITY - (ARE CONTAINERS USED IN STUDY IDENTICAL TO THOSE IN CONTAINER SECTION): The container/closure system used in the stability study is the same as those described in the container section.

LABELING: Pending

STERILIZATION VALIDATION: Acceptable per J.McVey 5/22/98.

SIZE OF BIO BATCH (FIRM'S SOURCE OF NDS OK?): See below.

SIZE OF STABILITY BATCHES - (IF DIFFERENT FROM BIO BATCH, WERE THEY MANUFACTURED VIA THE SAME PROCESS?):
Executed batch records for Lot #R037-021 (40 kg, vials filled and vials released; manufactured on 5/14/97) are submitted in support of production batch size of vials.

PROPOSED PRODUCTION BATCH - (MANUFACTURING PROCESS THE SAME AS BIO/STABILITY?): See above.

Specifications for active ingredient: Under #23A in chemist's review

Specifications for the finished product: Under #28 and #29 in chemist's review

CHEMIST: Maria C. Shih /S/ 8/27/98 **DATE:** 7/30/98
SUPERVISOR: John Harrison **DATE:**

/S/ for Harrison 8/26/98

1. CHEMIST'S REVIEW NO. #2

2. ANDA #65-002

3. NAME AND ADDRESS OF APPLICANT

American Pharmaceutical Partners, Inc.
Attention: Mitchall Clark
2045 N. Cornell Avenue
Melrose Park, IL 60160
Phone: 708-343-6100

(Formerly Fujisawa USA, Inc.)

4. LEGAL BASIS FOR SUBMISSION

21 CFR §442.218a (442.18a)

Reference drug: Zinacef® (sterile cefuroxime sodium) manufactured by Glaxo Wellcome

5. SUPPLEMENT(s)
N/A

6. PROPRIETARY NAME
N/A

7. NONPROPRIETARY NAME

Sterile Cefuroxime Sodium,
7.5 g/100 mL Pharmacy Bulk Package

8. SUPPLEMENT(s) PROVIDE(s) FOR:
N/A

9. AMENDMENTS AND OTHER DATES:

Original application: 12/16/97
FDA acknowledgment: 2/4/98
Correspondence: 1/20/98
Correspondence: 2/5/98 (constituted stability and compatibility study reports)
Correspondence: 2/26/98 (COAs for Nitrogen)

Correspondence: 6/1/98 (change in ownership)
Amendment 6/11/98 to NA letter 4/20/98 (MINOR)
Telephone Amendment 7/30/98

10. PHARMACOLOGICAL CATEGORY
Antibacterial

11. Rx or OTC
Rx

12. RELATED IND/NDA/DMF(s)

See also DMF List (None mentioned in Form 356h)

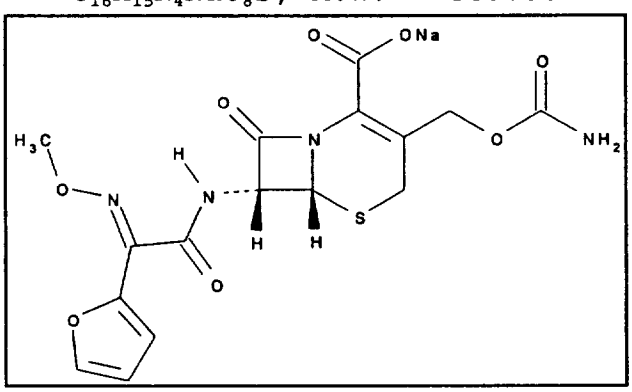
13. DOSAGE FORM
Sterile powder for injection
7.5 g/100 mL Pharmacy Bulk Package

14. POTENCY
7.5 g/100 mL Pharmacy Bulk Package

15. CHEMICAL NAME AND STRUCTURE

Cefuroxime Sodium USP

$C_{16}H_{15}N_4NaO_8S$; M.W. = 446.36



Sodium (6R,7R)-7-[2-(2-furyl)glyoxylamido]-3-(hydroxymethyl)-8-oxo-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylate, 7^2-(*Z*)-(*O*-methyloxime), carbamate (ester). CAS [56238-63-2]

16. RECORDS AND REPORTS
N/A

17. COMMENTS

Effective 6/1/98, the ownership of this ANDA is transferred from Fujisawa USA, Inc. To American Pharmaceutical Partners, Inc.(APP), 2825 Santa Monica Boulevard, Santa Monica, CA 90404.

In Amendment 6/11/98 Firm answers our concerns in order:

Q1. We note on page 212 under In-Process Controls, that the required release testing of the active ingredient was performed at

Fujisawa USA, Inc.
2045 N. Cornell Avenue
Melrose Park, IL 60160

Is this going to be the practice with the commercial production?

A1. The future release testing of the active ingredient will be performed at their manufacturing site:

American Pharmaceutical Partners, Inc.
3159 Staley Road
Grand Island, NY 14072

Release testing may also be done at the following sites:

1) American Pharmaceutical Partners, Inc. (APP)
2045 N. Cornell Avenue
Melrose Park, IL 60160

Q2. We note that you use the same drug substance for your ANDA in conventional vials, which when prepared for IM use at the concentration of 750 mg/3 mL, a suspension will form. We recommend a particle size distribution specification be included in the drug substance specifications. Please submit methodology and data.

A2. Firm uses to measure particle size distribution. Data from ten different lots are shown in Table 1 (D_{50} = 82 μm). They propose a particle size distribution specification: "NLT % of particles which are not greater than μm". It is not acceptable. Call was made to agent Lincy Michael (see Memo dated 7/27/98) asking for revision.

In Telephone Amendment 7/30/98, the particle size distribution specification is revised: % or greater of the particles LT μm; % or greater of the particles LT μm". Acceptable.

Q3. Please provide the procedures for selecting bulk lots when more than one bulk batch is used. Procedures for handling and storage of sterile bulk material after opening should be described. How long do you intend to keep the sterile bulk material? Describe the retest schedule.

A3. The selection is based on the potency (within 2%). Target fill weight is then calculated using the lowest potency of the selected raw material manufacturers lot.

Sterile bulk containers are opened and transferred to a lift system within the Class 100 area. The raw material is discharged from the bulk container into the filling unit until contents are exhausted. A new container is opened and transferred to the filling

unit, in the same manner as described above, until lot requirements are met.

After sterile bulk containers are opened, the raw material is connected to the filling equipment and drawn from until exhausted. All manipulations are conducted in the Class 100 work environment.

When sterile bulk material is released for production it is assigned a QC retest date (within two years for approved Grand island raw material, or within one year after the test date from another APP location). Testing is then performed annually until material depletion.

Q4. The stability report for the exhibit sample contains the whole spectrum of impurity profile as your proposed drug substance specifications. For Release and Stability specifications of the finished product, only two impurities and total impurities are tested. Please clarify.

A4. The current specifications include limits for DEFU, Cefuroxime Lactone, and Total Impurities. Anti-isomer Cefuroxime and 3-Acetoxy Cefuroxime are not included since they are not degradation products, but process related impurities carried over from the drug substance. Firm provided data to demonstrate that there is no significant increase in these two ingredients (Tables 3, 5, and 6).

Firm states that the total impurity limit was calculated by taking into account any impurity whose peak area was greater than the limit of quantitation.

Status Summary:

Labeling:	Under review
Microbiology:	Acceptable 5/22/98
Bio:	Waiver granted 3/27/98

EER: Acceptable 2/17/98
Sample: Not requested (USP drug)

18. CONCLUSIONS AND RECOMMENDATIONS
Approval recommended (pending labeling)

19. REVIEWER: DATE COMPLETED:
Maria C. Shih 7/30/98

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65002

MICROBIOLOGY REVIEW

OFFICE OF GENERIC DRUGS
Microbiologists Review #1
May 13, 1998

A. 1. ANDA: **65-002**
APPLICANT: Fujisawa USA, Inc.
2045 North Cornell Avenue
Melrose Park, IL 60160-4429
Attn. Donald E. Baker

2. PRODUCT NAME: **Sterile Cefuroxime Sodium**

3. DOSAGE FORM AND ROUTE OF ADMINISTRATION: Sterile powder for Injection. **7.5g/100 mL, Pharmacy Bulk Pack.**

4. METHOD(S) OF STERILIZATION:

5. PHARMACOLOGICAL CATEGORY: Antibiotics

B. 1. DATE OF INITIAL SUBMISSION: Letter Dated **December 16, 1997,** Acknowledged **February 4, 1998.**

2. DATE OF AMENDMENT: NA

3. RELATED DOCUMENTS:
DMF
was approved in 1985. ANDA 65-001 -conventional vials from same sterile bulk. DMF
DMF for Fujisawa, Grand Island, NY. updated Sept. 1997.

4. ASSIGNED FOR REVIEW: May 13, 1998.

C. REMARKS: Most of the sterilization data is located in DMF and was reviewed in November of 1997 and found acceptable. Verification was done that 100 mL vials are included in the previously reviewed validations.

D. CONCLUSIONS: The submission is **recommended for approval** on the basis of sterility assurance.

/S/ 5/19/98
James L. McVey

initialed by F. Fang or F. Holcombe 5/22/98

cc:
Original ANDA
Duplicate ANDA
Field Copy
drafted by: J. McVey 65002ap1.m

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65002

BIOEQUIVALENCY REVIEW(S)

BIOEQUIVALENCY COMMENTS

ANDA: 65-002 APPLICANT: Fujisawa

DRUG PRODUCT: Cefuroxime Sodium for intravenous infusion, 7.5 g/100 mL vial (pharmacy bulk package)

The Division of Bioequivalence has completed its review and has no further questions at this time.

Please note that the bioequivalency comments provided in this communication are preliminary. These comments are subject to revision after review of the entire application, upon consideration of the chemistry, manufacturing and controls, microbiology, labeling, or other scientific or regulatory issues. Please be advised that these reviews may result in the need for additional bioequivalency information and/or studies, or may result in a conclusion that the proposed formulation is not approvable.

Sincerely yours,

/S/

Dale Conner, Pharm. D.
Director, Division of Bioequivalence
Office of Generic Drugs
Center for Drug Evaluation and Research

Cefuroxime Sodium
Injection, 7.5 g/100 mL vial
(Pharmacy bulk package)
Reviewer: Gur J.P. Singh
ANDA 65-002
File # 65002W.D97

Fujisawa
Thee Parkway North
Deerfield, IL 60015
Submission Date:
December 16, 1997

REVIEW OF A WAIVER REQUEST

BACKGROUND: The firm is seeking waiver of *in vivo* bioequivalence study requirements for its cefuroxime sodium for intravenous infusion (7.5 g Base/100 mL vial). The reference product Zinacef® (Glaxo, NDA #50588) is also marketed in the same strength. It is indicated for treatment of a variety of infections.

COMPARATIVE COMPOSITION (Not to be released under FOI):

Ingredient	*Amount/vial*	
	Test	*Reference*
Cefuroxime Sodium	7.5 g Base	7.5 g Base

COMMENTS:

1. The test and reference product vials do not contain any inactive ingredients. The only inactive ingredient used is water for constitution.

2. The test product is eligible for the waiver of *in vivo* bioequivalence study requirements pursuant to 21 CFR Section 320.22(b)(1) of Bioavailability/Bioequivalence Regulations because:

    a. It is a parenteral solution (upon constitution) intended solely for injection.

    b. It contains the same active ingredient as a drug product that is subject of an approved full new drug application.

RECOMMENDATION

The Division of Bioequivalence agrees that the information submitted by Fujisawa demonstrates that cefuroxime sodium for intravenous infusion, 7.5 g/100 mL vial (pharmacy bulk package) falls under 21 CFR Section 320.22 (1) of Bioavailability/Bioequivalence Regulations. The waiver of *in vivo* bioequivalence study requirements for of cefuroxime sodium 7.5 g/100 mL vial of the test product is granted. From the Bioequivalence point of view, the Division of Bioequivalence deems the test formulation to be bioequivalent to Zinacef® 7.5 g/vial (pharmacy bulk package) manufactured by Glaxo.

Gur J.P. Singh, Ph.D. /S/
Division of Bioequivalence
Review Branch II.

RD INITIALED SNERURKAR
FT INITIALED SNERURKAR /S/ 3/27/1998

CONCUR: /S/ Date: 3/27/98
Dale P. Conner, Pharm.D
Director
Division of Bioequivalence.

GJP SINGH 3/20/98 65002W.D97
cc. ANDA # 65002, original, HFD-650 (Division Director), HFD-630 (OGD), HFC-130 (Jallen), HFD-600 (Hare), HFD-655 (Nerurkar, Singh), Drug file, Division file.

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

65002

CORRESPONDENCE

2.1 shih, M.

ANDAs

American Pharmaceutical Partners, Inc. JUL 10 1998
Attention: Mitchall G. Clark
2045 North Cornell Avenue
Melrose Park, IL 60160

Dear Sir:

We acknowledge receipt of your communication dated June 2, 1998, submitted as required by the provisions of Regulation 21 CFR 314.72(a) and Section 505(k) of the Federal Food, Drug and Cosmetic Act for the attached list of abbreviated applications.

Your letters details the transfer of ownership of these ANDAs, from Fujisawa USA, Inc. to American Pharmaceutical Partners, Inc.

Pursuant to 21 CFR 314.72(b), the new owner shall advise FDA about any change in the conditions of the pending applications.

The material submitted is being retained as part of your applications.

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

Attachment

ANDA 65-002

Fujisawa USA, Inc.
Attention: Donald E. Baker
3 Parkway North, 3rd Floor
Deerfield, IL 60015-2548

FEB 4 1998

Dear Sir:

We acknowledge the receipt of your abbreviated new drug application submitted pursuant to Section 505(j) of the Federal Food, Drug and Cosmetic Act.

Reference is also made to the telephone conversation and your facsimile dated January 13, 1998.

NAME OF DRUG: Cefuroxime Sodium for Injection USP, ~~7.5g (base)~~/vial, Pharmacy Bulk Package

Name ?

DATE OF APPLICATION: December 16, 1997

DATE (RECEIVED) ACCEPTABLE FOR FILING: December 17, 1997

We will correspond with you further after we have had the opportunity to review the application.

Please identify any communications concerning this application with the ANDA number shown above.

Should you have questions concerning this application, contact:

Mark Anderson
Project Manager
(301) 827-5848

Sincerely yours,

/S/

Jerry Phillips
Director
Division of Labeling and Program Support
Office of Generic Drugs
Center for Drug Evaluation and Research

FUJISAWA USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

December 16, 1997

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: Cefuroxime For Injection, USP (PBP)
7.5 g/100 mL vial

Dear Mr. Sporn:

Fujisawa USA, Inc. is submitting an Abbreviated Antibiotic Drug Application (an archival and review copy) in accordance with Section 507 of the Federal Food, Drug and Cosmetic Act to seek approval to market Cefuroxime For Injection, USP. Also, enclosed are three copies of the analytical methods and validation section for the drug substance and finished dosage form. In addition, a field copy has been sent to the FDA Buffalo District Office in accordance with 21 CFR §314.94(d)(5). Fujisawa USA, Inc. certifies that the field copy is a true copy of the Abbreviated Antibiotic Drug Application submitted herewith. Also, note that the single dose vial package application is being submitted to the FDA simultaneously with this pharmacy bulk package application.

Fujisawa USA, Inc. will manufacture this product at 3159 Staley Road, Grand Island, NY 14072. This application contains information describing the manufacturing and control of Cefuroxime For Injection, USP 7.5 g/100 mL vial using a stopper and a Type I USP glass vial. Applicable general procedural approaches and data may be cross-referenced to Fujisawa USA, Inc. DMF

In addition, this application contains a request for the waiver of *in vivo* bioequivalence studies.

This application has been formatted according to the information in Office of Generic Drugs Policy and Procedure Guide #30-91, April 10, 1991 and letters to industry dated October 14, 1994 and December 24, 1996. An executive summary explaining the organization of this application is included after the cover letter. Please note that the USP nomenclature "Cefuroxime For Injection, USP" and "Cefuroxime Sodium, USP" is being used in this application as this USP nomenclature will become effective in May 1998.

Please do not hesitate to contact me at **(847) 317-1088** or facsimile number **(847) 317-7286** or Mr. Donald E. Baker at **(847) 317-8872** if you have any questions or require additional information concerning this application.

Sincerely,

Alexa L. Chun, Ph.D.
Manager, Regulatory Affairs

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AMERICAN PHARMACEUTICAL PARTNERS, INC.

ARCHIVAL

July 30, 1998

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

NDA ORIG AMENDMENT

N/Am

RE: ANDA 65-002
Cefuroxime For Injection, USP
7.5 g base/vial
Pharmacy Bulk Package
Manufacturing Site: Grand Island, NY

TELEPHONE AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application submitted on December 16, 1997 for the above mentioned drug product. References are also made to the telephone conversation between Ms. Maria Shih, FDA and Ms. Lincy Michael, American Pharmaceutical Partners, Inc. (APP) on 7/27/98 and 7/30/98. As requested by Ms. Shih, we have revised the specifications for particle size distribution. APP hereby submit the revised specifications for Cefuroxime Sodium bulk drug substance.

In compliance with 21 CFR 314.96(b), a true and complete field copy of this amendment is being submitted to the Acting District Director , Buffalo District, Food and Drug Administration, 599 Delaware Ave., Buffalo NY 14202.

Should you have any questions or require additional information concerning this application, please contact the undersigned at **(708) 547-3617.**

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist

RECEIVED
JUL 31 1998
GENERIC DRUGS

8.4.98

2045 NORTH CORNELL
MELROSE PARK, ILLINOIS 60160

TEL (708) 343-6100
FACSIMILE (708) 343-4269
WWW.AMPHARMAPARTNERS.COM

AMERICAN PHARMACEUTICAL PARTNERS, INC.

ARCHIVAL

June 11, 1998

N\ AM

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 65-002
Cefuroxime For Injection, USP
7.5 g base/vial
Pharmacy Bulk Package
Manufacturing Site: Grand Island, NY

MINOR AMENDMENT

Dear Mr. Sporn:

Reference is made to our Abbreviated New Drug Application submitted on December 16, 1997 for the above mentioned drug product. References are also made to the deficiency letter dated April 20, 1998 and the telephone conversation between Mr. John Harrison (FDA) and Ms. Alexa Chun (Fujisawa) on 5/19/98. We are responding to the observations noted in the deficiency letter and hereby submit this minor amendment. For ease of review, we have organized the FDA observations with the corresponding responses in the order as delineated in the letter.

Please note that the ownership of this application was transferred from Fujisawa USA, Inc. to American Pharmaceutical Partners, Inc. effective June 1, 1998.

In compliance with 21 CFR 314.96(b), a true and complete field copy of this amendment is being submitted to the Acting District Director , Buffalo District, Food and Drug Administration, 599 Delaware Ave., Buffalo NY 14202.

Should you have any questions or require additional information concerning this application, please contact the undersigned at **(708) 547-3617** or Mitchall G. Clark at **(310) 264-7768.**

Sincerely,

Lincy Michael

Lincy Michael
Senior Regulatory Scientist

RECEIVED
JUN 12 1998
GENERIC DRUGS

2045 NORTH CORNELL
MELROSE PARK, ILLINOIS 60160

TEL (708) 343-6100
FACSIMILE (708) 343-4269
WWW.AMPHARMAPARTNERS.COM

AMERICAN PHARMACEUTICAL PARTNERS, INC.

RETURN RECEIPT REQUESTED

June 2, 1998

Douglas Sporn, Director
Office of Generic Drugs
FDA, CDER
HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773

NEW CORRESP.
NC

AADA 65-002
Cefuroxime for Injection, USP (Pharmacy Bulk Package)
Change in Ownership of the Pending Application

Dear Mr. Sporn:

Reference is made to Fujisawa USA, Inc.'s (FUSA) Abbreviated Antibiotic Drug Application for Cefuroxime for Injection, USP, AADA 65-002, which is currently pending approval. Further reference is made to FUSA's letter dated June 1, 1998 advising the Agency that effective June 1, 1998, the ownership of this application has been transferred to American Pharmaceutical Partners, Inc. (APP). The corporate address for American Pharmaceutical Partners, Inc., is 2825 Santa Monica Boulevard, Santa Monica, CA 90404.

In accordance with 21CFR§314.72, we hereby advise you that American Pharmaceutical Partners, Inc. accepts ownership of this application. We commit to agreements, promises and conditions made by FUSA and contained in the application. American Pharmaceutical Partners, Inc. has a complete copy of the approved application, including supplements and records that are required to be kept under section 21CFR§314.81.

The new company name will be included in the product labeling and submitted in an upcoming amendment.

All FDA correspondence should be forwarded to the following address:

Genny Cruz, Senior Regulatory Scientist
American Pharmaceutical Partners, Inc.
2045 North Cornell Avenue
Melrose Park, IL 60160

If you have any questions concerning this submission, please do not hesitate to contact me at (310)264-7768 or (708)343-6100. Our fax number is (708)343-4269.

Yours faithfully,

M G Clark

Mitchall G. Clark,
Senior Director, Regulatory Affairs

H:\DATA\RA\APP\TRANSFER\CEFUROXI.002

RECEIVED
JUN 08 1998
GENERIC DRUGS

2045 NORTH CORNELL
MELROSE PARK, ILLINOIS 60160

TEL (708) 343-6100
FACSIMILE (708) 343-4269
WWW.AMPHARMAPARTNERS.COM

ARCHIVAL

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Telephone (847) 317-8800 • Telefax (847) 317-7286

Fujisawa

June 1, 1998

NEW CORRESP

Douglas Sporn, Director
Office of Generic Drugs
Food and Drug Administration
Center for Drug Evaluation and Review
HFD-600, Room 150
7500 Standish Place
Rockville, MD 20855-2773

RE: ANDA 65-002
Cefuroxime for Injection, USP Sterile
(Pharmacy Bulk Package)
Pending Approval

CHANGE IN OWNERSHIP OF AN APPLICATION

Dear Mr. Sporn:

In accordance with the provisions of 21 CFR 314.72, the ownership of the above identified ANDA is being transferred in its entirety, effective June 1, 1998, from Fujisawa USA, Inc. (FUSA) to American Pharmaceutical Partners, Inc., 2825 Santa Monica Boulevard, Santa Monica, CA 90404. (APP)

FUSA affirms that all of the rights to the referenced ANDA have been transferred to APP and that a complete copy of the ANDA including all amendments and FDA correspondence have been provided to APP.

The name and address of the new primary contact person at APP is:

COPORATE ADDRESS
Mitchall Clark
Senior Director, Regulatory Affairs
American Pharmaceutical Partners, Inc.
2825 Santa Monica Boulevard
Santa Monica, CA 90404
Phone: (310) 264-7768

CORRESPONDENCE ADDRESS
Mitchall Clark
Senior Director, Regulatory Affairs
American Pharmaceutical Partners, Inc.
2045 N. Cornell Avenue
Melrose Park, IL 60160
Phone: (708)343-6100

All FDA correspondence should be forwarded to the correspondence address.

Please change your records to reflect this change in the ownership of the A DA andacknowledge receipt of this letter. All future communications regarding this ANDA should be sent to APP.

Sincerely,

Jerry D. Johnson

Jerry D. Johnson, Ph.D.
Vice President, Regulatory Affairs and Pharmacovigilance

RECEIVED
JUN 0 2 1998
FDA/CDER

cc: Mitchall Clark
Senior Director, Regulatory Affairs (APP)

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ARCHIVAL

Fujisawa USA, Inc.
Parkway North Center, Three Parkway North
Deerfield, Illinois 60015-2548
Tel. (847) 317-1088 • Telefax (847) 317-7286

Fujisawa

Alexa L. Chun, Ph.D.

Manager
Regulatory Affairs

NEW CORRESP
NC

NDA Mfg. 3/12/98

February 26, 1998

Douglas Sporn, Director
Office of Generic Drugs
Metro Park North II, HFD-600, Room 150
Center for Drug Evaluation and Research
Food and Drug Administration
7500 Standish Place
Rockville, MD 20855-2773

Re: Cefuroxime For Injection
SVP ANDA# 65-001, PBP ANDA# 65-002
Nitrogen Vial Flush

Dear Mr. Sporn:

Reference is made to our abbreviated new drug applications 65-001 and 65-002 submitted to the FDA on December 16, 1997, and a teleconference with Mr. Mahmud on February 23, 1998. In that teleconference I referred to a prior teleconference with Mr. Mahmud (January 7, 1998) where I had confirmed that there were no inactive ingredients in the Cefuroxime For Injection, USP ANDAs. Subsequently, I was informed that nitrogen was used as a vial flush to purge oxygen from the vials. However, nitrogen was not included as an inactive ingredient; there is no specification for nitrogen in the Cefuroxime For Injection, USP product codes.

As per my conversation with Mr. Mahmud on February 23, 1998, I am providing the manufacturer's Certificate of Analyses for nitrogen (Attachment 1) and Fujisawa USA's Certificate of Analyses for nitrogen (Attachment 2).

Please do not hesitate to call me if you have any questions.

Sincerely,

Alexa L. Chun, Ph.D.

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